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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/049,666
Filing Date: February 15, 2002
Appellant(s): SUZUKI ET AL.

Gregory T. Lowen
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 6-28-2011 appealing from the Office action mailed 10-29-2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims on appeal are 44, 46, 47 and 48.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

EP 0847 992	SUZUKI	6-1998
5,681,584	SAVASTANO	10-1997
7,041,313	DIETRICH	5-2006
5,962,454	UEDA	10-1999
5,665,348	OKAYAMA	9-1997
5,500,422	ITO	3-1996

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 44 and 46-48 are rejected under 35 U.S.C. l03 (a) as being unpatentable over EP 0847 992 by itself or in combination with Savastano (5,681,584), further in view of Dietrich (7,041,313), Okayama (5,665,348), Ueda (5,962,454) individually or in combination.

According to instant claims, the formulation of the benzamide derivative contain

1) An excipient which is D-mannitol

2) A lubricant which is magnesium stearate

3) A disintegrant which is carboxy methyl starch sodium

4) At least one member selected from the group consisting of an amino compound and inorganic base: The inorganic base is sodium carbonate.

Claim 46 in addition recites polyethylene glycol.

EP teaches benzamide derivatives claimed by applicant (pages 5-44). Additionally, EP teaches that the active ingredient may be used in general pharmaceutical compositions, and may be prepared with generally used diluents or excipients, such as binders, extenders, fillers, moisturizers, disintegrants, surfactants, and lubricants. EP also teaches that the pharmaceutical dosage form can be a tablet, pill, powder, solution, suspension, emulsion, granules, capsule, injection or suppository. More specifically, EP teaches the use of lactose, ***calcium carbonate***, amino acids, ***starch***, methyl celluloses, calcium Carmellose, sugars, ***stearates***, talc, ***polyethylene***

glycol, sodium alginate and many other well-known excipients (page 46, lines 5- 39). The selection of appropriate excipients in combination with claimed benzamide derivative would have been obvious to one of ordinary skill in the art with a reasonable expectation of success, since EP is suggestive of these art known excipients together with the benzamide derivative. The examiner also points out that in tablets routinely contain, binders, disintegrants, lubricants and buffering substances such as carbonates and bicarbonates and choosing the appropriate compounds falling under each category with a reasonable expectation of success would have been obvious to one of ordinary skill in the art at the time the invention was made.

EP does not specifically teach mannitol, carboxymethyl starch and sodium carbonate.

Savastano while disclosing tablet formulations of Benzamide derivatives suggests that excipients such as mannitol, magnesium carbonate, binders such as carboxymethylcellulose be used. Savastano further teaches that suitable tablet lubricants include calcium stearate (col. 7, line 4 through col. 8, line 65).

Dietrich teaches the equivalency between sodium carboxymethylcellulose taught by Savastano and sodium carboxymethyl starch and starch and alginates taught by EP in tablet preparations (col. 2, lines 41-53. Dietrich further teaches the used of auxiliaries such as calcium stearates and mannitol as preferred filler (col. 2, lines 54-61).

Okayama similarly teaches the equivalency between carboxymethylcellulose and carboxymethylstarch and also the equivalency between sugars such as lactose and

mannitol and magnesium stearate and calcium stearate taught by Savastano. Okayama also teaches polyethylene glycol (col. 3, line 67 through col. 4, line 16).

Ueda similarly teaches the equivalency between carboxymethylcellulose and sodium carboxymethyl starch. Ueda also teaches the equivalency between calcium carbonate and sodium carbonate (col. 7, lines 10-29).

The use of mannitol, carboxymethyl starch, magnesium stearate and sodium carbonate in the compositions of EP would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the reference of Savastano is suggestive of the use of these excipients with other benzamide derivatives. Although Savastano does not teach magnesium salt of stearic acid or the use of sodium carbonate instead of magnesium carbonate, one of ordinary skill in the art would use any metal as the cationic part in these salts with the expectation of obtaining similar results and also because of the equivalency between magnesium stearate and calcium stearate taught by Okayama and the equivalency between calcium and sodium carbonates taught by Ueda. Although Savastano does not teach the use of carboxymethyl starch, one of ordinary skill in the art would be motivated to use this compound instead of carboxymethylcellulose because of the equivalency between these compounds as taught by Okayama and Ueda. As pointed out before, adjusting the pH of the composition with acids and bases to obtain the desired pH at which the benzamide derivatives are fully active without degradation is well within the skill of the art. ***Furthermore, as pointed out before, tablets routinely contain, binders, disintegrants, lubricants and buffering substances such as carbonates and***

bicarbonates and choosing the appropriate compounds falling under each category with a reasonable expectation of success would have been obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

Appellant's arguments have been fully considered, but are not found to be persuasive. Appellant argues that with respect to independent claim 44, the applied prior art does not teach or suggest a combination of a pharmaceutical formulation of a benzamide of Formula I or a pharmaceutically salt thereof, an excipient consisting of D-mannitol, a lubricant consisting of magnesium stearate, a disintegrant consisting of carboxymethylstarch sodium and at least one member selected from the group consisting of an amino compound and an inorganic base, wherein the amino compound is tris(hydroxymethyl)amino methane and the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate and potassium bicarbonate.

According to appellant, Suzuki merely provides a generalized and undifferentiated list of additives, such as those listed at page 46, which may potentially be used for pharmaceutical formulations of various types and point out to page 46, lines 9-16 of Suzuki. These arguments are not persuasive since in it is common practice in the art to include excipients, tablet binders, disintegrating agents, glidents (lubricant) and Suzuki teaches the commonly used tablet additives for the claimed benzamide compounds. The Examiner cites US 5,500,422 which shows the routinely used

components in combination with benzamide compounds (see col. 10, line 60 through col. 11, line 4 and Example 68) in this context. It is within the skill of the art to select the proper excipients, binders, glidants and disintegrating agents and therefore, the Examiner disagrees with appellant's arguments that without additional guidance a person of ordinary skill in the art would have no rationale for choosing between the distinct classes of compounds in the above listings of additives in Suzuki. In essence, although Suzuki does not teach these specific additives, he teaches the addition of sugars and mannitol is a sugar; Suzuki teaches carboxymethyl cellulose as a binder, but not carboxymethyl starch; however, tableting art recognizes carboxymethyl starch as a binder; Suzuki teaches calcium carbonate. Therefore, it is still the Examiner's position that although Suzuki does not teach the specific combination, one of ordinary skill in the art would carboxymethyl starch instead of carboxymethyl cellulose, mannitol as the sugar and sodium carbonate instead of calcium carbonate with a reasonable expectation of success.

Appellant argues that there would be no rationale for a person of ordinary skill in the art to prepare the particular formulations recited in claim 46 with only the knowledge of the teaching of Suzuki. More specifically as argued by appellant, a person of ordinary skill in the art would have no rationale for preparing a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically salt thereof in combination with at least one solvent that is polyethylene glycol; at least one of an organic acid salt selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate; at least one of an amino

compound selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine, L- glutamate, and carbachol; and at least one of an inorganic base selected from the group consisting of sodium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, disodium phosphate, and ammonia.

These arguments are not persuasive. Suzuki does teach polyethylene glycol on page 46. The examiner also points out that claim 46 recites, the Markush members, selected from the group consisting of an organic acid salt, an amino compound and an inorganic base and therefore, requires the presence of only one; one of them is sodium alginate and Suzuki does teach this compound.

With regard to the superior and unexpected properties with respect to the stability of the benzamide derivative against degradation argued by applicant (Table 1 in the brief), the examiner points out that the experiment was conducted with specific components with specific amounts whereas instant claims are drawn to the combination of several components. The results are not commensurate with the scope of the claims even with regard to the amounts of the excipients. Furthermore, the Examiner is unable to see how one can say that the differences observed are significant (no statistical evaluation was done), let alone 'unexpected'. Appellant argues that samples outside the scope of claim 44, i.e., a, e, f and g do not contain an additional amino compound or inorganic base and for this reason, they are less stable than the samples b, c and d in

that they result in a higher percentage of degradation products. These arguments are not persuasive since Suzuki does teach the inclusion of amino acids (instant claims recite arginine and glycine) and also quaternary ammonium base on page 46. The small increases in stability observed show only the proper pH requirement of the compound for its stability and it is a routine experimentation an artisan performs to obtain the best possible results.

Appellant's arguments to the above rejections based on the declaration by Masahiro Sakabe have been fully considered, but are not found to be persuasive. In his declaration, Masahiro Sakabe argues that he believes that an artisan skilled in the art of high-performance liquid chromatography (HPLC), the differences between the listed numbers are statistically significant. According to Sakabe Table 1 shows that when D-mannitol and compound I are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.21 percent (%) relative to the total amount of compound I present in the mixture and this value is comparable to the stability of compound 1 in the absence of any additional component (0.18 or 0.19 depending on the conditions tested). Further according to Sakabe in contrast, when lactose and compound I are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.55 percent (%) or 0.44 % relative to the total amount of compound 1 present in the mixture, depending on the particular conditions tested. Finally, Sakabe states that given his level of skill in HPLC chromatography, he believe that the difference between, for example, 0.21 (D-mannitol + compound 1) and 0.55 or 0.44 (lactose + compound 1) is statistically significant in that a conclusion may be drawn regarding the stabilizing effects of D-

mannitol on compound 1 and the destabilizing effects of lactose on compound I. These arguments are not persuasive. The examiner is not questioning the level of skill of Masahiro Sakabe with regard to HPLC. What Masahiro Sakabe is offering is his opinion with regard to Statistics, which is totally different from HPLC results. Any data obtained by any method or technique has to be analyzed statistically to evaluate the significance of the results. That means calculating the mean of a number of experiments and determine the standard deviation (or standard error) of the mean and analyze whether the differences observed between groups are statistically significant. Just looking at the data obtained and coming to a conclusion that the results are significant is deemed to be speculative. Furthermore, instant claims recite several members in each group of excipients, lubricants, disintegrants and inorganic base and the scope of the claims is not commensurate with the results obtained with lactose or mannitol. Finally it should be pointed out that the degradation values of the active agent observed with different excipients are so low and since the excipients, lubricants and disintegrants are known in tableting technology and the prior is suggestive of these agents, selecting the proper excipient, lubricant, disintegrating agent and an inorganic base to obtain the best suited combination for that particular active agent is deemed to be within the skill of the art. With regard to the superior results with formulations b, c and d argued by applicant (Table 2 results), a careful examinations shows that these formulations contain in addition, a buffer ingredient (tris (hydroxymethyaminomethane, potassium bicarbonate and potassium carbonate respectively) and since a compound's ability to remain stable depends on the pH at which it is stable, selection of an appropriate buffering agent such

as Tris, carbonates and bicarbonates would have been obvious to one of ordinary skill in the art. Furthermore, as pointed out above, there is no evidence of statistical evaluation of the results indicating their significance.

Appellant argues that the office action states that although Savstano does not teach the use of carboxymethyl starch, one of ordinary skill in the art would be motivated to use this compound instead of carboxymethylcellulose because of the equivalency between these compounds as taught by Okayama and Ueda and that they disagree with this asserted rejection. According to appellant, similar to Suzuki, Savastano contains undifferentiated lists of excipients. Appellant argues that while they acknowledge that Savastano lists mannitol as a suitable additive, Savastano also lists lactose as an equally suitable additive in the same sentence and as shown in Table 1 at page 11 of appellant's specification , lactose hastens degradation of a benzamide compound encompassed by appellant's claims 44 and 46.

These arguments are not persuasive. Appellant's arguments with regard to mannitol and lactose in Table 1 have been addressed by the Examiner above. Furthermore, appellant has not shown any unexpected results obtained by using carboxymethylstarch by comparison with starch taught by EP or carboxymethylcellulose taught by Savstano because these are art recognized disintegrants in tableting art.

In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was

within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellant argues that the dependent claims 47 and 48 are individually allowable at least because of their respective dependencies from independent claim 47 and for the reasons argued above. Appellant's arguments are not persuasive. Claim 47 recites the presence of polyethylene glycol (which is taught by EP) and adjusting the pH of the composition and claim 48 recites adjusting the pH of the composition. As pointed out before, adjusting the pH of the composition with acids and bases to obtain the desired pH at which the benzamide derivatives are fully active without degradation is well within the skill of the art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Gollamudi S. Kishore/

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